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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,014	INGELMAN-SUNDBERG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group 11, claim 7, a method for treating colon cancer, using a substance activated by the protein CYP2W1, in the reply filed on 07/10/07 is acknowledged.

The traversal is on the following ground(s): The cited art does not teach the single general inventive concept of present claims 1-10 and Groups 1-22. The teachings of Banki et al and Bendayan et al relate to different antibodies and provide no basis for asserting any inherent binding property in the polypeptides in either Becha et al or Asundi et al, which the Examiner asserts are 87% similar and 75% similar, respectively, to SEQ ID NO: 8.

Further, the Examiner has not shown that the homology of the polypeptides of Becha et al and/or Asundi et al in fact contain the necessary binding epitopes. While the sequences of Becha et al and Asundi et al are similar to N-terminal part of CYP2W1, namely amino acids 1-421 and 1-375, respectively, of a total of 490 amino acids, the present specification teaches that the antibodies should be raised against the C-terminal part of CYP2W1. Further, the antibodies were shown not to be cross-reactive with other P- 450 enzymes as described in the specification at page 15, lines 6-8. In fact, claim 1 recites that the compound comprises one part conferring "specific binding affinity" towards a CYP2W1 molecule according to SEQ I'D NO: 8. As noted in the art, this means that it should show substantially no binding affinity towards related proteins such as those dislosed by Becha et al and Asundi et al.

This is not found persuasive because of the following reasons:

1) The sequences taught by Becha et al and Asundi et al have 87% and 75% similarity, respectively, with the CYP2W1 SEQ ID NO:8 and seem to be the same as the claimed CYP2W1, as recited in claims 3-7, because CYP2W1 without being accompanied by a sequence identification number encompasses variant CYP2W1.

2) The claimed antibodies seem to be the same as the antibodies to the sequences taught by the art, because the limitation that the antibodies bind to the C-terminal region of SEQ ID NO:8 is not in the claims, and further, because the antibodies taught by the art would bind to an extensive number of shared epitopes, from amino acids1-421 and 1-375, respectively, from a total of 490 amino acids, in view of the antibody cross-reactivity phenomena, taught by Banki et al, and Bendayan et al.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group 11, claim 7, a method for treating colon cancer, using a substance activated by the protein CYP2W1. The embodiment of claim 7, as drawn to a method for treating cancer, using a substance inducing the enzyme CYP2W1, and/or the compound according to claim 1, has been withdrawn from consideration as being drawn to non-elected invention.

Sequence Rule

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the reasons set forth below:

The specification recites sequences without being accompanied by sequence identification numbers, for example, the figures 1, and 11 legends on page 2, and page 4 respectively, and the sequences cited on p. 8-10.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 7 is indefinite for the use of designation "CYP2W1" as the sole means of identifying the claimed enzyme. The use of laboratory designation only to identify a particular enzyme renders the claim indefinite because different laboratories may use the same laboratory designations to define completely distinct enzymes. Amendment of the claims to incorporate for example, a sequence identification number, to include physical and/or functional characteristics of "CYP2W1", which unambiguously define "CYP2W1", is suggested.

2. Claim 7 is indefinite, because claim 7 lacks a result to relate to the preamble. It is not clear how a substance activated by the enzyme CYP2W1 is effective in treating colon cancer. Is the activated substance toxic and capable of killing the cancer cells? Or does the activated substance trigger a certain signaling pathway?

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification asserts that the CYP2W1 SEQ ID NO:8 is a member of the cytochrome P450 CYP family (p.1, 4), and contemplates the use of the cytochrome P450 enzyme CYP2W1 and genetic variants thereof as a drug target in cancer therapy (p.4, item under Detailed description of the invention). The specification discloses that SEQ ID NO:8 contains some typical structure associated with P450, including a hydrophobic NH2-terminal, the proline-rich region and the conserved cysteine, which is the fifth heme iron ligand (p.12, lines 6-8). The specification discloses that enzymes within P450 family 2 with highest identity to CYP2W1 are CYP2D6 (42%) and CYP2S 1 (40%) (p.12, lines 14-15).

The specification, however, does not disclose the structure of CYP2W1 variants, nor the specific substances activated by the CYP2W1 SEQ ID NO:8.

Although several P450 cytochrome enzymes, such as CYP2D6, CYP2E1, CYP2B6, CYP2S 1, CYP3A4 are known in the art (the instant specification, p.1, and figure 2), the art does not discloses the structure of CYP2W1 or its variants, nor the specific substances activated by the CYP2W1 SEQ ID NO:8.

CYP2W1, without being accompanied by a sequence identification number, encompasses a **genus of CYP2W1** enzyme **variants**, with unknown structure and function. Further, "a

substance" activated by CYP2W1 encompasses a genus of compounds with unknown structure and function.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the

genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that □the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

In this case, the specification does not describe the CYP2W1 variant protein, or substance activated by CYP2W1 protein in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide sufficient structure or common structure, other than SEQ ID NO: 8, to support the broad breath of the claimed genus. Nor is there any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single protein, SEQ ID NO: 8, this

does not provide a description of the CYP2W1 variant protein, or substance activated by CYP2W1 protein, that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe the CYP2W1 variant protein, or substance activated by CYP2W1 protein, by the standards shown in the example in Lilly. The specification describes only a single protein, SEQ ID NO: 8. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The specification does not provide an adequate written description of the CYP2W1 variant protein, or substance activated by CYP2W1 protein, that is required to practice the claimed invention. Thus, the specification does not meet the 112, first paragraph written description requirement, and one of skill in the art would reasonably conclude that Applicant did not have possession of the claimed CYP2W1 variant protein, or substance activated by CYP2W1 protein at the time the invention was made. Since the specification fails to adequately describe the product for use in the claimed method, it also fails to adequately describe the claimed method.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The disclosure in the specification has been set forth above. The specification discloses that the mRNA encoding SEQ ID NO:8 is highly overexpressed in colon cancer tissue as compared to normal colon tissue (table 1 on pages 13-14, and p.16). The specification discloses that SEQ ID NO:8 has high expression level in the cell line HepG2 (p.17). The specification further discloses that some cytochrome P450 proteins have the ability to activate prodrugs to cytotoxic products (p.1, lines 20-28, bridging p.2). The specification discloses, for example, metabolic activation of acetaminophen to a reactive imine that cause liver hepatotoxicity by the cytochrome P450 members CYP2E1 and CYP3A4, or activation of prodrugs in cancer therapy, such as cyclophosphamide or ifosfamide, by the cytochrome P450 member CYP2B6. The

specification contemplates improving drug targeting to tumor cells by administering substances or prodrugs that can be metabolically activated to a cytotoxic and/or anti-cancer drug by SEQ ID NO:8.

The specification, however, does not have any data or objective evidence that SEQ ID NO:8 has the enzyme function of members of cytochrome P450 family. The specification does not have any data or objective evidence that a prodrug could be metabolically activated by SEQ ID NO:8 in colon cancer, such that colon cancer is effectively treated.

1. Claim 7 is rejected under 112, first paragraph for lack of enablement for a method of **treating colon cancer,** using **a substance activated** by the enzyme CYP2W1.

One cannot predict that SEQ ID NO:8 has the enzyme function of members of cytochrome P450 family, and could metabolically activate a prodrug in colon cancer, such that colon cancer is effectively treated, because of the following reasons: 1) The art acknowledges that function cannot be predicted based solely on structural similarity to a protein or motifs thereof found in the sequence databases, and 2) Cancer therapy is highly unpredictable.

Unpredictability of function prediction, when based solely on sequence or motifs similarity.

One cannot predict that SEQ ID NO:8 is a member of the cytochrome P450 family, and having drug or prodrug metabolizing function of members of the cytochrome P450 family, based solely on its sequence similarity with some members of the cytochrome P450 family, or the presence of a hydrophobic NH2-terminal, the proline-rich region and the conserved cysteine, which is the fifth heme iron ligand. Although SEQ ID NO:8 has 42% or 40% similarity with cytochrome P450 members CYP2D6 and CYP2S 1, respectively, there is a 58% or 60%

dissimilarity between SEQ ID NO: 8 and cytochrome P450 members CYP2D6 and CYP2S 1, respectively, and the effects of these dissimilarities upon protein function cannot be predicted, in view of the unpredictability of protein chemistry. As an example, there is no indication, nor one can predict that a sequence taught by the art, WO 200290521-A2, which is 87% similar to SEQ ID NO8 (MPSRCH search result, 2007, us-10-532-014.8.rag, result 2, pages 1-2, of record) has the property and function of cytochrome P450 proteins. Bowie (Science, 1990, 257:1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie further teaches that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47

with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

Further, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein or motifs thereof found in the sequence databases. For example, Ofran Y et al, 2005 (Drug Discovery Today, 10 (21): 1475-1482), in a review of methods for predicting protein-function by homology, teach that homology based prediction of a protein function (homology-based annotation transfer) is one of the main source of incorrect functional annotations that occur in databases, and is inaccurate and limited, and that the function of only less than 35% of all proteins could be predicted automatically, when accepting errors of less than or equal 5% (p.1476, second column, item under "Drug discovery and protein-function prediction, and p.1478, first column, last paragraph, under "Although powerful, homology-based transfer is inaccurate and limited", bridging second column). Skolnick et al, 2000 (Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork, 2000 (Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Similarly, Barlett et al, 2003 (In: Structural Bioinformatics, Bourne et al, eds, Wiley-Liss, Inc., pages 387-407) teach that it is not always that family members will have related functions, as shown by the classic example of divergence

of function within the homologous family of lysozyme and alpha-lactalbumin, and as shown by the diverse function of 31 enzyme superfamilies (p.395, item under "Homologous families and function", and p.397, first paragraph). Barlett et al further teach that when structure motifs are used for predicting protein function, such as in the case of enzymes, detailed knowledge of the active site is required (p.399, last paragraph). Rost et al, 2003 (Cell Mol Life Sciences, 60: 2637-2650) teach that using sequence homology to predict protein function is problematic and limited in scope (abstract, p.2641). Rost et al further teach that using known sequence motifs for predicting function is not always successful, because of the difficulty in predicting structure around the site, and considerable variation of consensus sequences, as for the case of phosphorylation site and kinase substrate specificity, respectively (p.2643, first column, last paragraph). In the instant application, the specification does not teach whether the domains commonly found in members of the cytochrome P450 family, a hydrophobic NH2-terminal, the proline-rich region and the conserved cysteine, which is the fifth heme iron ligand, are sufficient to confer the properties of metabolic activation of prodrugs into a cytotoxic compound.

Thus, in view of a lack of sufficient disclosure in the specification, and further in view that structural similarity, or domain similarity cannot be predictably used for predicting a protein function, one cannot predict that the protein SEQ ID NO:8 has function of members of cytochrome P450 family, and could metabolically activate a prodrug in colon cancer, such that colon cancer is effectively treated. Further, since the function of SEQ ID NO:8 is unpredictable, one cannot predict which of the claimed numerous substance are activated by SEQ ID NO:8.

Unpredictability of cancer treatment

It is well known in the art that cancer treatment is highly unpredictable. Kirkin et al, 1998, APMIS, 106 : 665-679, teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and in particular peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Boon, 1992 (Adv Can Res, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches that even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells, such as loss of tumor antigen (p.198, first paragraph). Smith RT, 1994 (Clin Immunol, 41(4): 841-849), teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Bodey et al, 2000, Anticancer Res, 20: 2665-2676, confirm the teaching of Boon and Smith, by

explaining the reasons for failure of vaccine in human. Bodey et al teach that although general immune activation against the target antigens has been documented in most cases, reduction of tumor load has not been frequently observed in human patients (abstract, second column, p.2673). Bodey et al teach that the failure of cancer vaccine is due to natural selection of highly aggressive clones in the treated patient, said clones no longer express the cancer specific antigen (abstract, second column, p.2673). Bodey et al teach that these clones of tumor cells survive the immune system, through secretion of immunoinhibitory cytokines, downregulation of MHC, loss of costimulatory molecules, and induction of T cell anergy (p.2673, second column, last paragraph).

Further, Gura, 1997, (Science, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain, 1994 (Sci. Am., 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti, 1993 (Crit. Rev. in Oncology/Hematology, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as

yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

2. Claim 7 is also rejected under 112, first paragraph, for lack of enablement for **variant CYP2W1 proteins**.

Applicants have not shown how to make and use the claimed CYP2W1 polypeptide variants which are capable of functioning as that which is being disclosed, in view of that protein chemistry is unpredictable, and that even a single amino acid substitution or what appear to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein, based on the teaching of Bowie, Burgess et al , and Lazar et al, supra.

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 13, 2007

/Larry R. Helms/

Supervisory Patent Examiner